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Title page

Title: Prevention of food allergy: can we stop the rise of IgE mediated food allergies?

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Foundation Trust, in partnership with the King's College London and King's College Hospital NHS Foundation Trust.

Structured Abstract

Purpose of review: Food allergy has become more prevalent in recent decades. Without a curative treatment for food allergy, prevention is key. Can we intervene and halt the food allergy epidemic?

Recent findings: There are three main hypotheses to explain the rise in food allergy: the dual-allergen exposure hypothesis, the hygiene hypothesis and the vitamin D hypothesis. In a recent systematic review of randomized controlled trials, only introduction of allergenic foods, namely egg and peanut, in the diet at the time of weaning and avoidance of temporary supplementation with cow's milk formula in the first few days of life showed low to moderate evidence of a preventative effect.

Summary: For primary prevention, introduction of allergenic foods at the time of weaning and avoidance of temporary supplementation with cow's milk formula in the first few days of life has been recommended. Introduction of foods once allergy has been excluded may be beneficial for sensitized subjects (secondary prevention). Once food allergy has been established, it is important to minimise complications (tertiary prevention) through allergen avoidance, timely treatment of allergic reactions, control of atopic co-morbidities and dietetic and psychological support, as appropriate. Immunomodulatory treatments can potentially be disease-modifying and require further research.

Abstract word count: 199

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Introduction

Food allergy affects about 8% of children in Western countries (1, 2) and its prevalence is increasing in the adult age group (3), probably reflecting both an increase in incidence and in life-time prevalence as children grow older. Food allergy has also been rising in other parts of the world, like South East Asia and Africa, particularly in urban centres (4, 5). Hospital admissions for food allergy and severity of food allergy have also increased, with a recent US study showing that about 40% of food allergic children have multiple food allergies, severe food allergies and have been prescribed an adrenaline auto-injector (1). Although many food allergies resolve spontaneously, others can be life-long. The 4-year follow-up of the Healthnuts cohort from Melbourne in Australia showed that the prevalence of food allergy decreased from 11% at 1 year to 3.8% at 4 years of age (6). The Schoolnuts study, in the same geographical area, showed a prevalence of food allergy of 4.5% at 10-14 years of age (7). The natural history of food allergy seems to be changing over time with more recent studies reporting a later acquisition of tolerance than previously, although such reports can be influenced by the population studied, the type of food allergy (e.g. whether IgE or non-IgE-mediated) and the approach adopted to assess resolution. Over the past few decades, we have witnessed an increase in the prevalence, severity and persistence of food allergy overall.

Why is the world becoming more allergic to food?

There are 3 main working hypotheses to explain the food allergy epidemic (**Figure 1**):

- Dual allergen exposure hypothesis
- Hygiene hypothesis
- Vitamin D hypothesis

Dual allergen exposure hypothesis

Atopic eczema is probably the main risk factor for food allergy, particularly early onset moderate-severe eczema (8, 9). The dual allergen exposure hypothesis, proposed by Gideon Lack in 1996, postulates that the development of food allergy results from the combination of time, route and dose of exposure to food allergens in early life (10). The balance between exposure through the gastro-intestinal tract, which is tolerogenic, particularly in high doses, and exposure through the skin, particularly to low doses of allergen through abraded inflamed skin affected with eczema, determines food allergy risk. When exposure via the gastrointestinal tract happens before exposure through the skin, tolerance is established; conversely, when exposure via the skin happens before the food is introduced in the diet, food allergy can develop. The dual allergen exposure hypothesis was tested in the Learning Early About Peanut Allergy (LEAP) randomized controlled trial (RCT), which demonstrated that early peanut consumption, from age 4-11 months, prevented the development of peanut allergy by the age of 5 years with 81% relative reduction in the prevalence of peanut allergy (11). This effect was sustained after 1 year of peanut avoidance, suggesting that the preventative effects were long-lasting (12). The higher prevalence of peanut allergy in the avoidance arm was evident immunologically with peanut avoiders having larger wheals on skin prick testing to peanut, higher prevalence of high peanut and Ara h 2-specific IgE levels and higher proportion of activated basophils, with basophil activation being inversely correlated with ratios of IgG4/IgE to peanut (11-13).

Hygiene hypothesis

The hygiene hypothesis was proposed by David Strachan in the 1989 following the observation that children from larger families had less asthma and allergic rhinitis. For food allergies, number of siblings and dog ownership have been identified as protective factors, probably

100 related to greater microbial exposure (14, 15). The gut microbiome has been implicated in the
101 development of food allergy and available evidence has recently been reviewed (16). With oral
102 tolerance developing in the gut, commensal microbiota can modulate immune development
103 and are required for a healthy immune response to foods (17). Observational studies in humans
104 have showed different microbiota between food allergic and non-allergic individuals and
105 between food allergic children who resolve their food allergies and children with persistent
106 food allergies (18-21). Studies in mouse models have demonstrated that intestinal microbiota
107 can transfer susceptibility or resistance to the development of food allergy, supporting its
108 implication in this condition, and have shed light on the mechanisms of their effects (17, 22).
109 Such mechanistic studies have allowed to understand the modifications to the immune system
110 induced by the microbiota and to identify key regulatory cells induced in the GALT as a
111 consequence of the introduction of solid foods in the diet, confirming that both the microbiota
112 and allergen exposure are required for the establishment of oral tolerance to foods.
113
114 *Vitamin D hypothesis*
115 Observational studies have documented a greater prevalence of reported food allergies, of
116 emergency visits for food allergic reactions and of prescriptions of adrenaline auto-injectors in
117 geographical areas with lower sun exposure (23). In the Healthnuts study, vitamin D
118 insufficiency was more common in infants with food allergy, with or without eczema,
119 compared to infants with eczema only and to infants with neither eczema nor food allergy (24).
120 Vitamin D insufficiency was also more common in children with multiple food allergies
121 compared to children with a single food allergy (24). However, vitamin D levels can be
122 influenced by various factors, including vitamin D binding protein levels and genetic
123 polymorphisms influencing vitamin D metabolism, which can explain the conflict with results
124 of other studies (25). A recent systematic review of the literature failed to find evidence to

support vitamin D supplementation in pregnancy (1 RCT and 1 observational study), lactation (0 studies), infancy (1 observational study) and childhood (0 studies) for primary food allergy prevention (26). Further studies are needed, possibly with patient stratification according to genotype and taking into account other factors affecting vitamin D levels (23).

Can we stop the food allergy epidemic?

With the alarming increase in prevalence, severity and persistence of food allergy and in the absence of a curative treatment, the hope of changing the current burden of food allergy is on prevention. There are three levels of prevention to consider:

- Primary prevention, i.e. reducing food allergy before allergic sensitisation develops;
- Secondary prevention, i.e. reducing food allergy after allergic sensitisation but before clinical food allergy develops;
- Tertiary prevention, i.e. minimising the consequences of clinical food allergy.

Primary prevention

Recently, a task force of the European Academy of Allergy and Clinical Immunology (EAACI) published a systematic review of RCT covering various interventions that could possibly modify the food allergy risk in the first year of life (27), namely food allergen ingestion during pregnancy or lactation, breastfeeding, milk formulas (standard cow's milk formula, hydrolysed formulas, soy-based formulas), introduction of complementary foods, vitamin supplementation, ingestion of fish oil, prebiotics, probiotics and synbiotics, application of emmolients, prophylactic allergen immunotherapy and BCG vaccination. From the available evidence, the only interventions that showed an effect with low to moderate certainty were the ones related to the introduction of allergenic foods in the diet. Introducing cooked egg and peanut in the diet at weaning (cooked egg from 6 months and peanut from median 7.8 months)

led to an absolute reduction in the prevalence of egg (29%) and peanut (12-23%) allergies with a moderate certainty of effect (28). Avoiding temporary supplementation with standard cow's milk formula in the first week of life was estimated to reduce in 6% the prevalence of cow's milk allergy with low certainty of effect (28).

Based on this systematic review, the EAACI will be soon publishing the guidelines for the prevention of food allergy. Recommendations (**Table 1**) include:

- No avoidance of food allergens during pregnancy or breastfeeding;
- Avoidance of temporary supplementation with cow's milk formula in the first week of life;
- Introduction of well-cooked egg in the infant's diet during weaning;
- Introduction of peanut in the infant's diet during weaning in populations with a high prevalence of peanut allergy.

No recommendations could be made about vitamin or fish oil supplementation, the use of prebiotics, probiotics or synbiotics, emmolients, prophylactic use of allergen-specific immunotherapy or BCG vaccination with the view of preventing the development of food allergy. Other systematic reviews support these recommendations (29, 30). Various studies are ongoing to try to gather high-quality evidence on the effect of interventions on food allergy risk, including RCT of high-allergen diet in the second half of pregnancy and first 4 months of lactation (e.g. peanut and egg in PrEggNut RCT), perinatal administration of probiotics (NCT00200954), ceramide-based emollient (e.g. PEBBLES RCT, NCT03667651), proactive treatment of atopic eczema (e.g. SEAL RCT), introduction of cashew and other tree nuts in the infants' diet (e.g. Cashew RCT, TreEat RCT), vitamin D supplementation (e.g. Vitality RCT, NCT02112734), whole cell pertussis vaccine instead of acellular pertussis vaccine (e.g. Optimum RCT) and BCG vaccination compared to placebo (e.g. MIS BAIR RCT).

Secondary prevention

What can be done to prevent food allergy in infants and children who are already sensitized? Considering the current recommendations in, for instance, Europe (27), USA (31) and Australia (32) (**Table 1**), the main intervention to prevent food allergy in sensitized infants and children is the introduction of allergenic foods in the diet, in the case that they are not allergic to them. In the LEAP study (11), the preventative effect of early peanut consumption was indeed observed in the SPT-positive stratum, although with a lower relative risk reduction compared to the SPT-negative stratum (70% versus 86%, respectively). However, data is absent for infants with SPT of 5 mm or greater as they were excluded from the LEAP study at screening, as they were likely to already have developed peanut allergy (33).

Most guidelines do not recommend allergy testing prior to introduction of the food, due to the eventual need for supervised challenges and the fact that limited resources could cause a delay in the food introduction, which could be counterproductive due to rapid immune changes in the first few months of life and consequent risk of developing food allergy (34, 35). However, the US guidelines recommend testing of high-risk infants prior to peanut introduction and also underscore the importance of being particularly proactive in this subgroup of infants, recommending peanut consumption from 4-6 months of age, whereas for the low risk group the introduction of peanut could be left to after 6 months, depending on the importance of peanut in the family's diet (31).

From the Allergist's perspective, for the family's that seek our advice prior to food introduction, it is justified to test for the foods that are commonly involved in food allergy in children and that the infant or child as yet to be exposed to via the oral route. This is particularly important for peanut in children with early onset severe eczema and/or egg allergy, as we have high-quality evidence with the LEAP study that early consumption of peanut is protective. The use of SPT and specific IgE testing should be based on a consciously defined pre-test

probability and interpreted with caution, based on existing studies on the predictive values of SPT and specific IgE in infants and young children as much as possible (**Table 2**). In children younger than 2 years of age, lower levels of IgE and smaller weals on SPT are more likely to be clinically relevant as reflected by the lower levels for 95% PPV cut-offs and the shift in the curves for the probability of clinical reactivity for a given IgE level compared to older children (36-38). As new modalities of testing are being developed like the basophil activation test, optimal cut-offs seem to be different in this age group and further research is needed (Santos AF, unpublished). Allergy testing prior to weaning should be done with the possibility of offering families supervised introduction of foods, in the office or the hospital setting, depending on the risk of reactivity. This is particularly important in this age group as immunological changes can happen quite rapidly in the first few months of life and the risk of food allergy can change from one assessment to the other. For this reason, ideally, there would be priority access for food challenges for infants as part of specialized Allergy services.

Tertiary prevention

In the cases where food allergy could not be prevented, it is important to minimise the impact of food allergy in the lives of children and their families, the risk of accidental allergic reactions and the progression and complications that could arise from food allergy and accompanying atopic comorbidities (39-41). Following an accurate and definitive diagnosis of food allergy, it is important to recommend appropriate allergen avoidance and emergency medication to treat allergic reactions in the context of accidental allergen exposure. Keeping good control of asthma (and also allergic rhinitis and eczema) is very important as more severe reactions can develop in food allergic children with uncontrolled asthma. Education of patients and family about the nature of food allergies, reading labels and good communication with school, peers and family is paramount. The support of a specialised dietitian is invaluable to advise on the

practical management of food allergy, appropriate replacement foods and adequate nutrient intake. Support from a clinical psychologist may also be beneficial in case of significant anxiety, depression or other mental health issues of child and/or family related with food allergies.

A definitive treatment of food allergy is highly expected. Immunomodulatory treatments have been investigated to try to modify the course of the disease and shut down the aberrant IgE-mediated immune response to foods. Allergen immunotherapy (AIT) has shown to increase the threshold of clinical reactivity while on treatment (desensitisation) with a subset of patients sustaining this effect following discontinuation of treatment (sustained unresponsiveness) (42-44). The foods that have been studied the most are peanut, egg and cow's milk. As AIT involves the administration of allergen to allergic patients, it incurs on a significant risk of allergic reactions during up-dosing and also during the maintenance phase, usually in the presence of co-factors, such as exercise, infection, menstruation and sleep deprivation (45). Some patients do not tolerate the side-effects and end up abandoning the treatment. Epicutaneous have a better safety profile than sublingual oral immunotherapy but the dose of allergen administered and the dose tolerated increase in reverse order. The administration of anti-IgE omalizumab concomitantly with AIT reduces the rate of adverse events and allows more rapid updosing. Active research on omalizumab (e.g. OUtMATCH, NCT03881696) and other anti-IgE molecules, dupilumab (anti-IL4R – e.g. NCT03793608, NCT03682770, NCT04148352) and etokimab (anti-IL33) (46) in food allergy is being pursued, at different stages of development. Long-lasting disease-modifying effect of immunomodulatory treatments are yet to be demonstrated.

Conclusion:

Food allergy is a significant public health problem and its increase seems to be related to environmental factors related to the Western modern life-style. The main hypothesis to explain this increase in food allergy prevalence, severity and persistence are the timing, dosing and route of exposure to food allergens in infancy, microbial exposure in early life and levels of vitamin D and possibly other factors. High quality evidence is lacking for many possible interventions to modify the food allergy risk. The main recommendation currently to prevent food allergy is to introduce allergenic foods in the infant's diet alongside with breastfeeding as exposure to food allergens via the oral route is necessary for the establishment of oral tolerance and can be protective. Future research needs to focus on the search not only for evidence of interventions for food allergy prevention but also for definitive treatments for food allergy.

Key points:

- Food allergy affects 8% of children and 11% of adults and its prevalence, severity and persistence has increased over time.
- For primary prevention of food allergy, introduction of allergenic foods, namely cooked egg and peanut, during weaning alongside breastfeeding is the main recommendation.
- Immunomodulatory treatments, such as allergen-specific immunotherapy and biologics, have been explored and further research into curative treatments for food allergy is needed.

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Tables

Table 1. Recommendations of major Allergy societies for primary prevention of food allergy.

Geographical location	Recommendations	Reference
Europe	• No avoidance of allergenic foods during pregnancy or breastfeeding. • Avoidance of temporary administration of standard cow's milk formula in the first days of life. • Introduction of cooked egg and peanut (the latter in populations with high prevalence of peanut allergy) during weaning.	(27)
USA	Introduction of peanut during weaning: • for infants with severe eczema and/or egg allergy at 4-6 months with consideration given to prior SPT/specific IgE testing • for infants with mild/moderate eczema around 6 months of age • for infants without eczema or food allergy, according to family's diet and preferences	(31)
Australia	• Weaning between 4-6 months, starting with iron-rich foods, while continuing breast-feeding. • Introduction of allergenic foods during weaning for all infants, including peanut butter, cooked egg, dairy, and wheat. • Hydrolyzed (partially or extensively) infant formula is not recommended for the prevention of allergic disease.	(32)

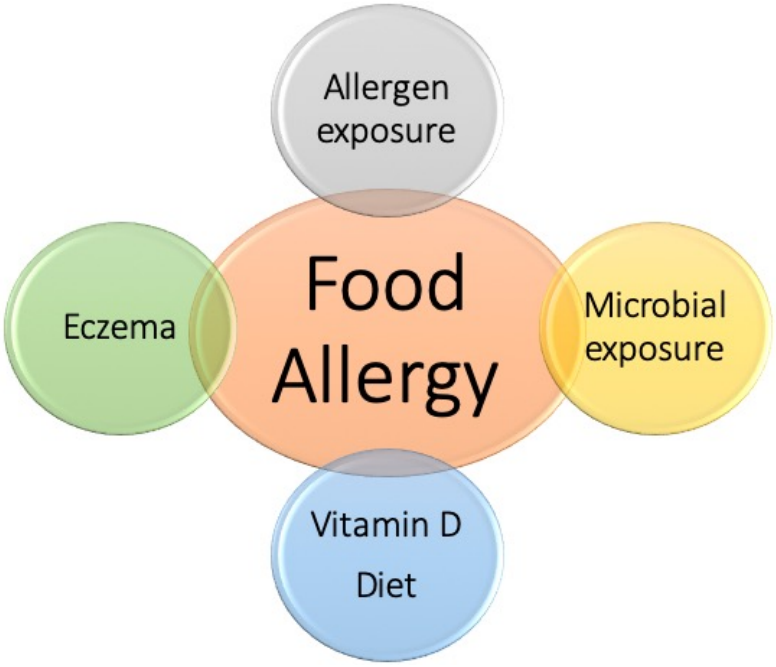
288 **Table 2.** Positive predictive value (PPV) cut-offs for skin prick test (100% PPV) and specific
289 IgE (95% PPV) to diagnose common food allergies in infants and young children (38). ND,
290 not determined.
291

Food	SPT	Specific IgE
Cow's milk	6 mm	5 KU/L
Egg	4 mm	2 KU/L
Peanut	4 mm	ND

292
293
294

Figure Legends:

Figure 1. Main hypotheses to explain the rise in food allergy in recent decades



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Notes on references:

Gupta 2018

**Recent questionnaire-based study performed in the USA providing recent data for prevalence and severity of food allergy in children.*

Gupta 2019

**Recent questionnaire-based study performed in the USA providing recent data for prevalence of food allergy in adults.*

Grimshaw 2020

**Data from Europrevall birth cohort studies establishing moderate-severe eczema as a major risk factor for food allergy.*

Marrs 2019

**Data from the EAT study in the UK demonstrating that dog ownership is a protective factor for the development of food allergy.*

B 2019

**Excellent recent review on the evidence for the role of the microbiome in food allergy.*

Feehley 2019

***Study in mouse models colonised with microbiome from healthy infants and infants with cow's milk allergy related specific bacteria in the ileum with protective and regulatory effects.*

Abdel-Gadir 2019

**Study using mouse models identified a population of regulatory T cells induced as a result of bacteriotherapy to reverse dysbiosis and suppress food allergy.*

Silva 2020

***Systematic review of randomized controlled trials of interventions aiming to prevent the development of food allergy, which formed the basis to the soon-to-be-published EAACI Guidelines for food allergy prevention.*

U 2019

***Randomized controlled trial demonstrating that supplementation with cow's milk formula in the first few days of life increases the risk of cow's milk allergy.*

Roberts 2019

***Meta-analyses of studies of early introduction of allergenic foods demonstrates the benefits of eary introducton of egg and peanut (but not milk) in the prevention of food allergy.*

Pajno 2018

***EAACI Guidelines on allergen-specific immunotherapy for food allergy recommending oral immunotherapy for peanut, egg and cow's milk for children older than 4 years of age with persistent allergies to induce dessensitization, which should be undertaken only in specialized centres with the appropriate resources to treat anaphylaxis and ensure patient safety during treatment.*

Chu 2019

***Systematic review and meta-analyses showing that patients submitted to oral peanut immunotherapy suffer more allergic reactions and anaphylaxis that those treated with placebo.*